

REMARKS

10015184.11601

The empty bracket symbol, "()", is widely used in medicinal chemistry to refer to methylene homologues (CH₂). The Declaration of Dr. Xiao-Xiong Zhou testifies to this fact. In addition, he provides evidence that this is an accepted convention by submitting patent abstracts obtained from the Derwent patent abstract service. Here it is evident that the empty bracket symbol is so commonplace that no additional definition of the symbol is provided, only the numeric values that are given for the associated subscript. The Examiner will also note that one of the numeric values given is "0." This value indicates that no methylene is present or, stated differently, that the flanking portions of the formula are linked by a single bond. The Applicants also follow this convention in the instant application. Thus, Applicants respectfully submit that the Specification and the Claims in their unamended form provided the essential structural cooperative relationships between the elements. The current amendment to the Specification only replaces one accepted convention with another.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly solicited.

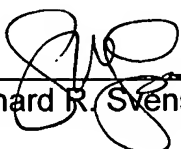
Attached hereto is a marked-up version of the changes made to the application by this Amendment.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Leonard R. Svensson (Reg. 30,330) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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for Leonard R. Svensson, #30,330

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Falls Church, VA 22040-0747
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LRS/SWG/lmt
1718-0194P

Attachments

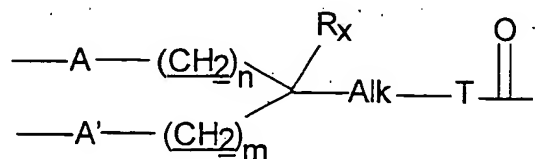
(Rev. 09/27/01)

10015134-11601

VERSION WITH MARKINGS TO SHOW CHANGES MADEIn the Specification:

The paragraph beginning on page 5, line 1, has been amended as follows:

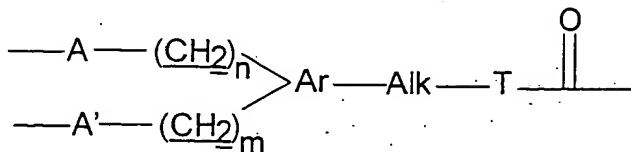
Useful trifunctional L₁ group, especially for esterifying directly to the nucleoside include linkers of the formula IIa or IIb:



IIa

where A and A' define a respective ester linkage between an hydroxy on the linker and the carboxy on R₁ or R₂ or an ester linkage between a carboxy on the linker and the hydroxy on R₁ as a fatty alcohol, or an amide linkage between an amine on the linker and a carboxy on R₁ or R₂, or an amide linkage between a carboxy on the linker and an amine on R₁ or R₂, or one of A and A' is as defined and the other is hydroxy, amino or carboxy in the event that R₁ itself is a free hydroxy, amino or carboxy group.

The paragraph beginning on page 6, line 1, has been amended as follows:

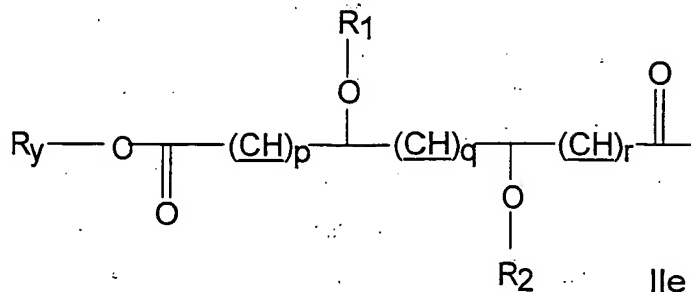


IIb

where

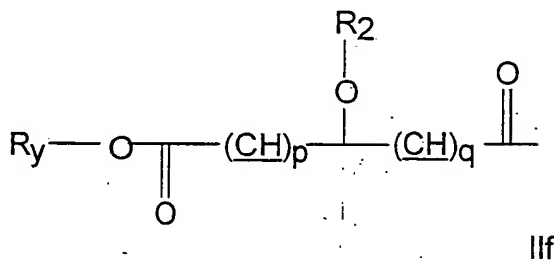
Ar is a saturated or unsaturated, preferably monocyclic carbo- or heterocycle with 5 or 6 ring atoms; and
A, A', T, Alk, m and n are as defined above.

The paragraph beginning on page 9, line 8, has been amended as follows:
Favoured linkers of the tartaric acid series above can be generically depicted as
Formula IIe:



and isomers where R_1 and R_2 are reversed, where R_1 and R_2 are as shown above, p , q and r are each independently 0 to 5, preferably 0 or 1 and R_y is the free acid, an R_1 ester or a conventional pharmaceutically acceptable carboxy protecting group, such as the methyl, benzyl or especially the ethyl ester.

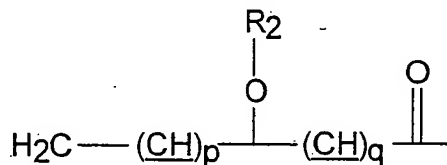
The paragraph beginning on page 9, line 20, has been amended as follows:
Favoured linkers of the malic series have the formula II f:



where R_y , p , q and R_2 are as defined above, preferably those where p and q are zero.

Page 12, has been amended as follows:

example on the β -carbon. In this embodiment the fatty acid of R_1 is esterified directly on the 5'-hydroxy (or equivalent) function of the nucleoside, generally with the R_2 group already esterified/amide bonded thereon. Alternatively, the functionalised fatty acid (the carboxy/hydroxy/amino function being appropriately protected) can be first esterified to the nucleoside and deprotected prior to coupling with R_2 . Linkers in accordance with a preferred embodiment of this aspect have the formula IId:



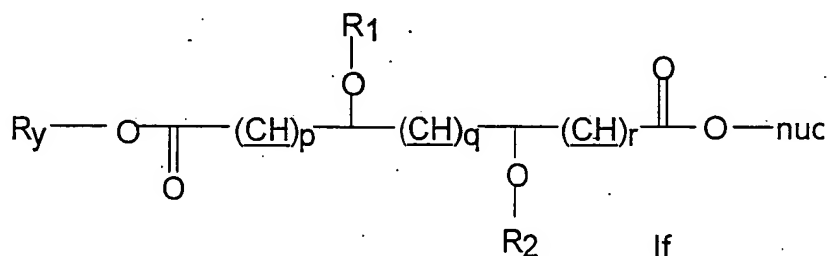
IId

where R_2 is the residue of an aliphatic L-amino acid and, p is 0, 1 or 2-20 (optionally including a double bond) and q is 0-5, preferably 0. Representative compounds include:

- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-butyryl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-hexanoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-octanoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-decanoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-dodecanoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-myristoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-palmitoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-stearoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-docosanoyl] guanosine,
- 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-valyloxy)-eicosanoyl] guanosine

2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-butyryl] guanosine,
 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-hexanoyl] guanosine,
 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-octanoyl] guanosine,
 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-decanoyl] guanosine,
 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-dodecanoyl] guanosine,
 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-myristoyl] guanosine,
 2',3'-dideoxy-3'-fluoro-5-O-[2-(L-isoleucyloxy)-palmitoyl] guanosine,

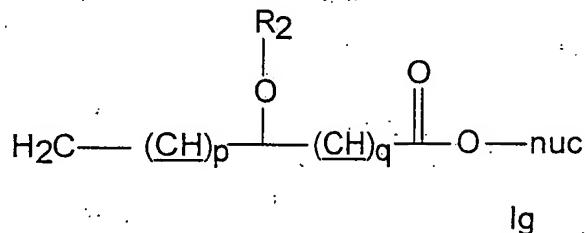
The paragraph beginning on page 21, line 1, has been amended as follows:



where R_1 , R_2 , R_y , p , q , r and o-nuc are as defined above.

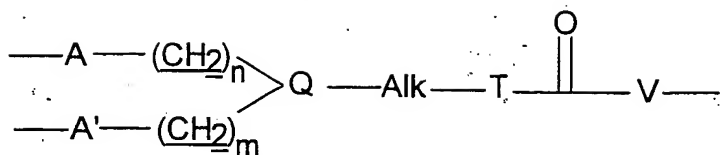
The paragraph beginning on page 22, line 1, has been amended as follows:

The invention also extends to compounds of the formula Ig

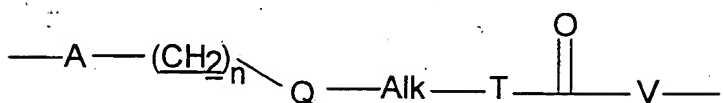


where R_2 , p , q and O-nuc are as defined above.

The paragraph beginning on page 43, line 1, has been amended as follows:



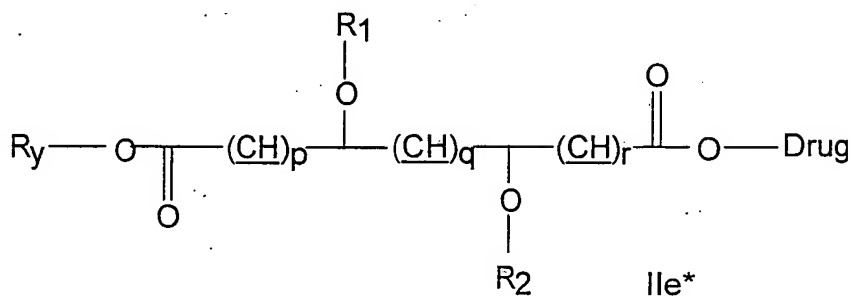
IIaa



II'aa

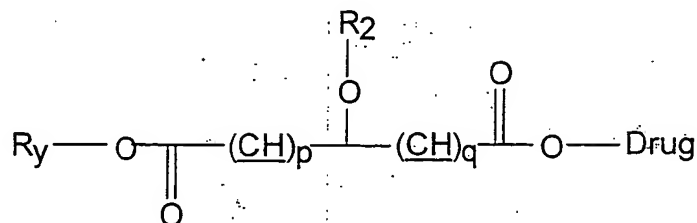
where A and A' are independently

The paragraph beginning on page 44, line 1, has been amended as follows:
formula II e*, that is



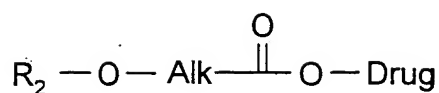
IIe*

formula II f*, that is



II f*

Formula Id*, that is

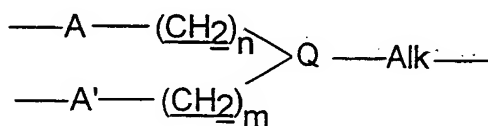


Id*

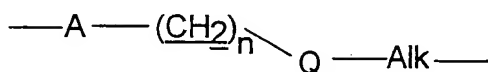
Page 45 has been amended as follows:

Where the Drug comprises a carboxyl function, the linker may comprise a structure of the formulae VIII or VIII':

where A, A', Q, Alk, m, and n are as defined for Formula IIaa & II'aa.

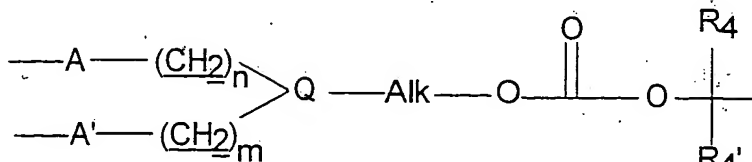


VIII

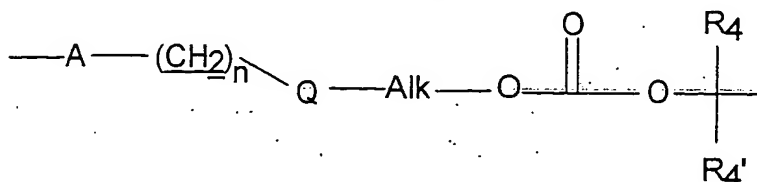


VIII'

Preferably, however, when the Drug comprises a carboxy function, the di- or trifunctional linker group L is a structure of Formulae IIdd or II'dd (that is a compound of Formulae IIaa or II'aa, wherein T is O and V is a structure of the formula IIbb):



IIdd

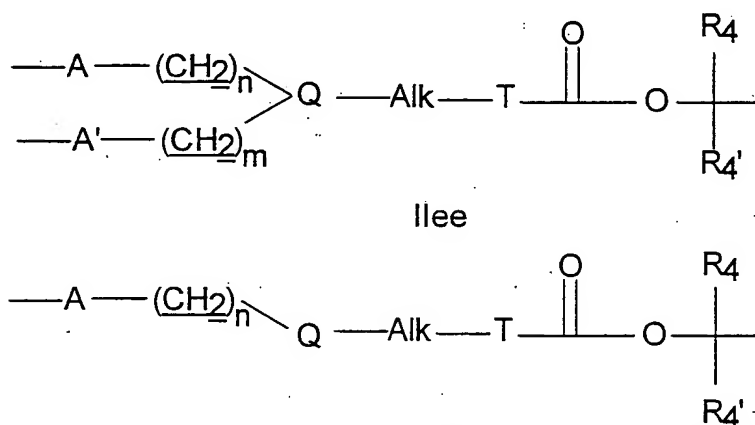


II'dd

In structure IId, R₄' is preferably hydrogen and R₄ is ethyl, phenyl, and especially methyl or hydrogen or R₄ and R₄' together define isopropyl

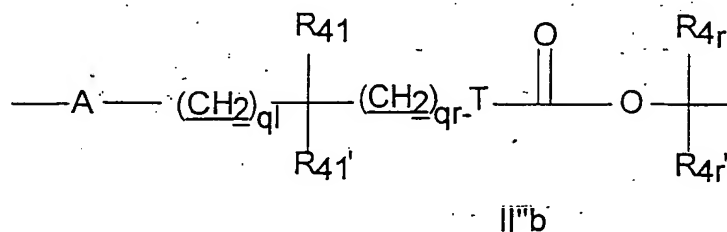
Page 46 has been amended as follows:

Where the Drug comprises a phosphoryl, phosphinyl or phosphonyl function, the di- or trifunctional linker group L may comprise a structure of the formula IIa or II'aa, especially those of the formula IIee or II'ee:



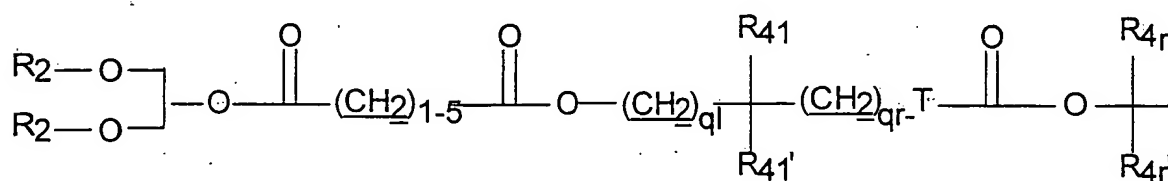
where T is a bond, -NH- or -O- and Q and A are as defined above including the cyclic Q structures such as cycloalkyl, phenyl and heterocycles such as furyl, pyridyl etc. In structures IIee and II'ee, R₄' is preferably hydrogen and R₄ is methyl, ethyl, phenyl and especially hydrogen or R₄ and R₄' define isopropyl.

Preferably, however, where the Drug comprises a phosphonyl, phosphinyl or phosphoryl function, the difunctional linker comprises a structure of the formula II''b:

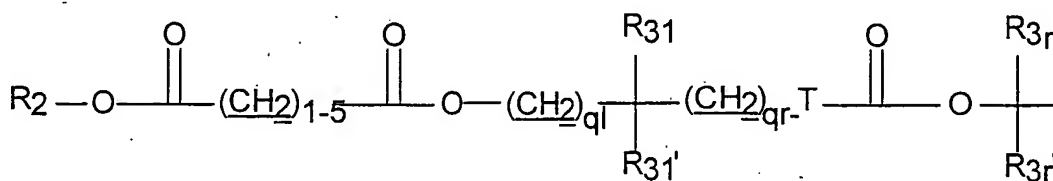


where T is a bond, -O- or -NH-, R_{4l} , R_{4r} and R_{4l}' and R_{4r}' are independently H or C_1 - C_3 alkyl and A is as defined above (or wherein A is a further difunctional linker to

The paragraph beginning on page 47, line 1, has been amended as follows: which one or more R_2 depends as described above). Examples of structures belonging to the latter possibility for A include those of Formula Va and Vb:



Va

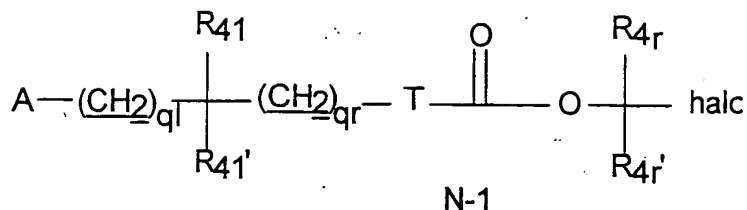


Vb

where T, q, R_2 , R_{4l} , R_{4l}' , R_{4r} and R_{4r}' are as defined above. Although formulae Va and Vb depict the dicarboxylate moiety as unbranched, it will be apparent that a wide variety of dicarboxylates will be suitable here, including branched and/or unsaturated and/or substituted dicarboxylic acid derivatives or various lengths, as described in more detail above.

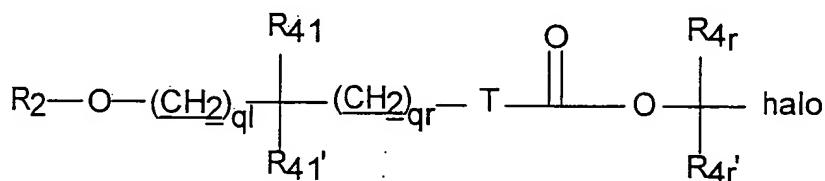
The paragraph beginning on page 48, line 23, has been amended as follows:

A further aspect of the invention comprises novel intermediates useful in applying structures of the formulae II'b to a drug and having the formula N-1:

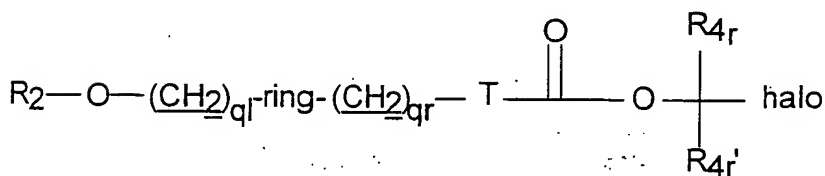


where A, q, R₄, R₄' and T are as defined for formula II''b.

The paragraph beginning on page 49, line 1, has been amended as follows:
A particularly preferred group of compounds substantially within formula N-1 are those of the formula N-2



or



N-2

where

R₂ is the acyl residue of an aliphatic amino acid,

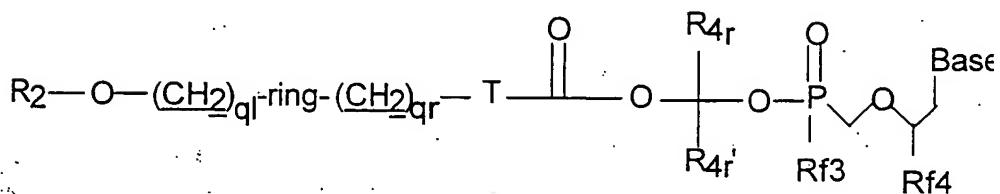
R_{3L} and R_{3L}' are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl phenyl or benzyl;

R_{3R} and R_{3R}' are independently H or C₁₋₃ alkyl

R₃ is H or C₁₋₃alkyl;

"ring" is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle; and halo is bromo, chloro or iodo.

The paragraph beginning on page 61, line 1, has been amended as follows:
Taking the phosphonate antivirals adefovir and cidofovir as examples, prodrugs
of the invention can be applied as shown in Formula PF2:



R₂ is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L'} are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R'} are independently H, C₁₋₃ alkyl or phenyl

ql is 0-3, qr is 0-3,

T is a bond, -NR₄- or -O-

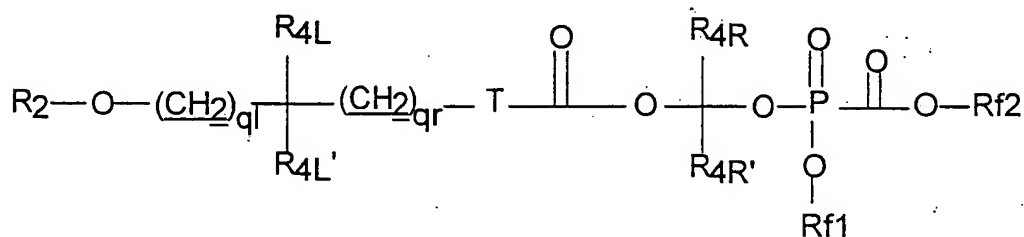
R₄ is H or C₁₋₃alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle;

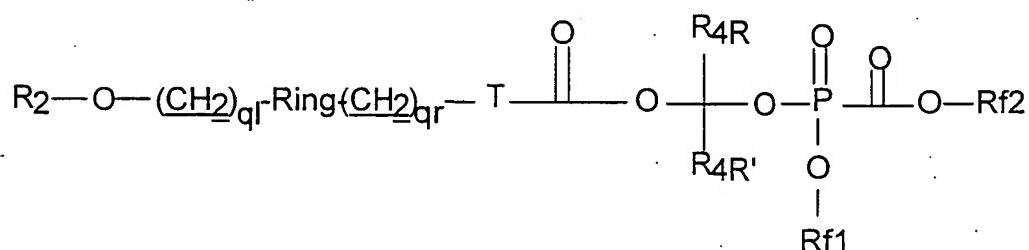
base is a natural or unnatural nucleotide base, especially guanine, adenine or cytosine,

Rf3 is H or a further structure of the formula II''b and Rf4 is H or CH₂OH.

The paragraph beginning on page 65, line 1, has been amended as follows:



or



where

R_2 is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L'} are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl, phenyl or benzyl,

R_{4R} and R_{4R'} are independently H, C₁₋₃ alkyl or phenyl

ql is 0-3, qr is 0-3,

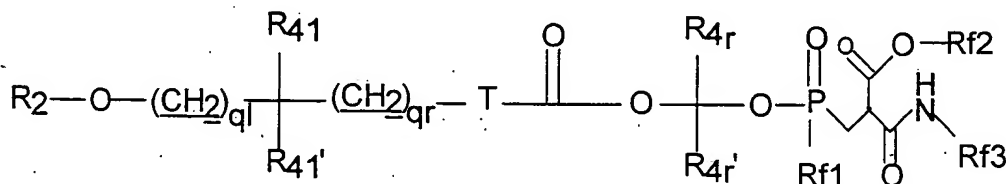
T is a bond, -NR₄- or -O-

R₄ is H or C₁₋₃alkyl;

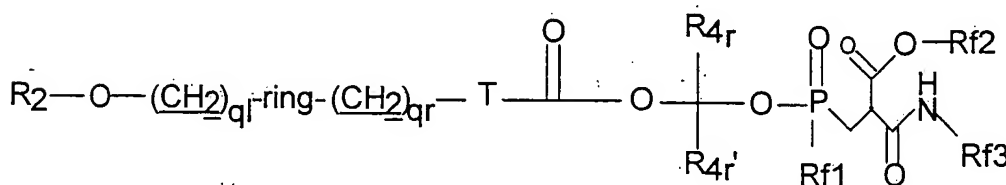
ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

and Rf1 is H or a further ester of formula II^b and Rf2 is H or a conventional pharmaceutically acceptable ester.

The paragraph beginning on page 68, line 1, has been amended as follows:



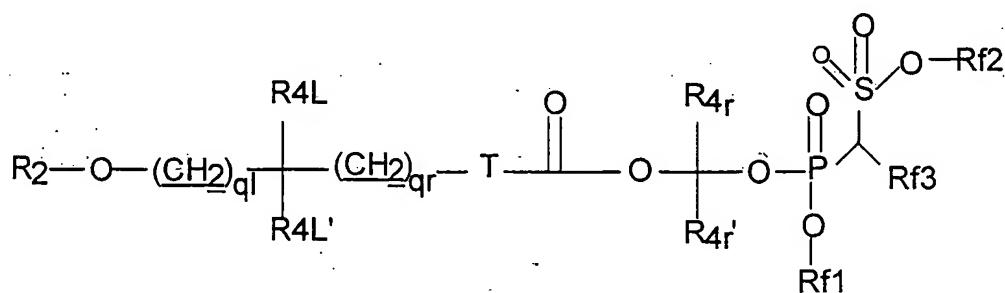
or



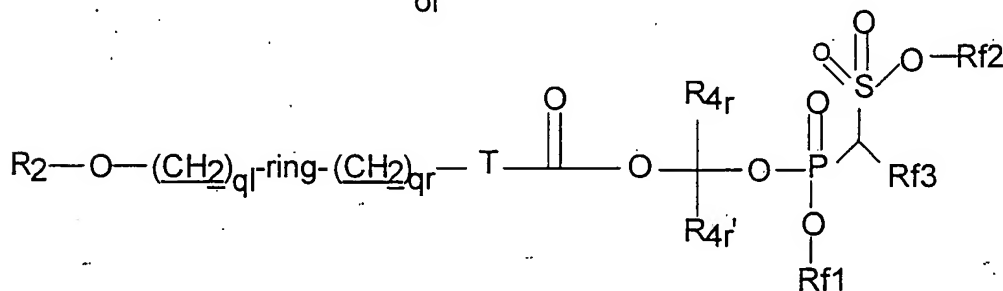
where Rf1 is H or a further structure of formula II^b
 Rf2 is H or a conventional pharmaceutically acceptable ester,
 Rf3 is a polyunsaturated, branched C₆₋₂₂ alkyl,
 R₂ is the acyl residue of an aliphatic amino acid,
 R₄₁ and R_{41'} are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-C₁C₆cycloalkyl, phenyl or benzyl,
 R_{4r} and R_{4r'} are independently H, C₁₋₃ alkyl or phenyl
 ql is 0-3, qr is 0-3,
 T is a bond, -NR₄- or -O-
 R₄ is H or C₁₋₃alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero- or carbocycle.

The paragraph beginning on page 69, line 4, has been amended as follows:
Other structurally similar phosphonates include α -phosphonosulphonates such as squalene synthase inhibitors of the formula PF5:



or



where

RF1 is H or a further structure of formula II^b

Rf2 is H or a conventional pharmaceutically acceptable ester a further

structure of formula II^b

Rf3 is a polyunsaturated, branched C₆₋₂₂ alkyl,

R₂ is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L'} are independently H, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkyl-C₁C₆cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R'} are independently H, C₁₋₃ alkyl or phenyl

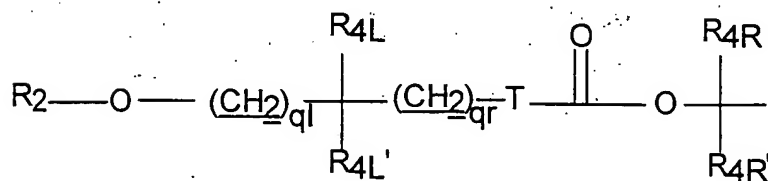
ql is 0-3, qr is 0-3,

T is a bond, -NR₄- or -O-

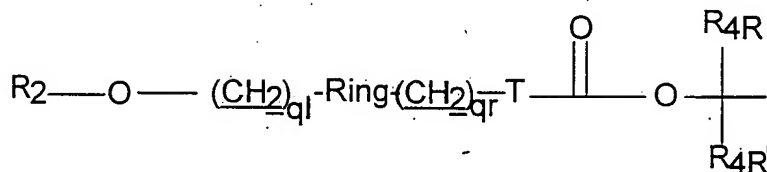
R₄ is H or C₁₋₃alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle.

The paragraph beginning on page 73, line 1, has been amended as follows:



or



where

R₂ is the acyl residue of an aliphatic amino acid,

R_{4L} and R_{4L'} are independently H, C₁₋₃ alkyl, C₃₋₆cycloalkyl, C₁₋₃alkyl-

C₁C₆cycloalkyl phenyl or benzyl,

R_{4R} and R_{4R'} are independently H or C₁₋₃ alkyl

ql is 0-3, qr is 0-3,

T is a bond, -NR₄- or -O-

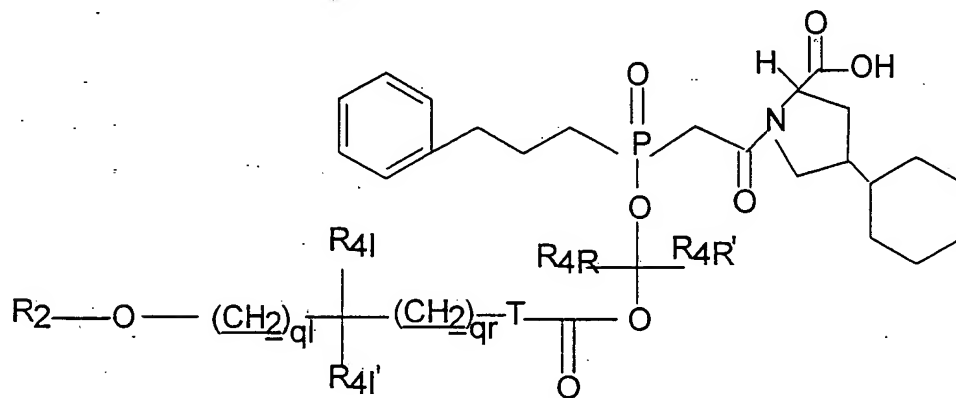
R₄ is H or C₁₋₃alkyl;

ring is an optionally substituted aromatic or non-aromatic, hetero-or carbocycle;

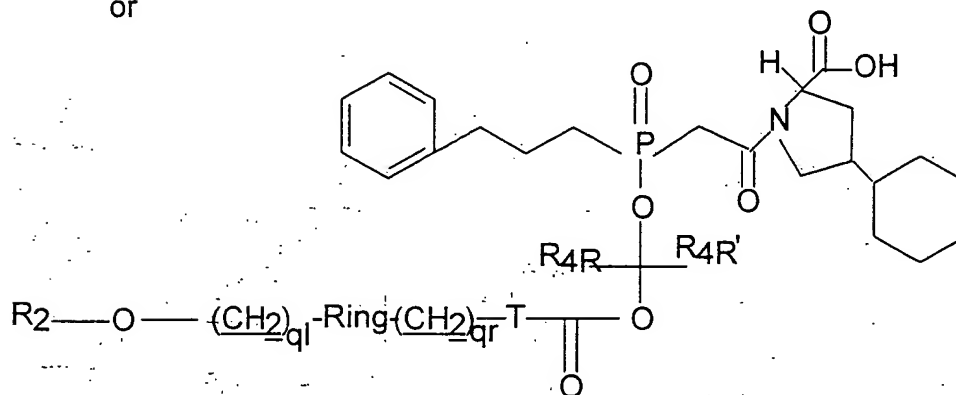
and the remainder of R₄1-4 are hydrogen or conventional pharmaceutically acceptable esters.

The paragraph beginning on page 85, line 16, has been amended as follows:

A still further preferred group of prodrugs of the invention are those based on fosinoprilate having the formula PF3:

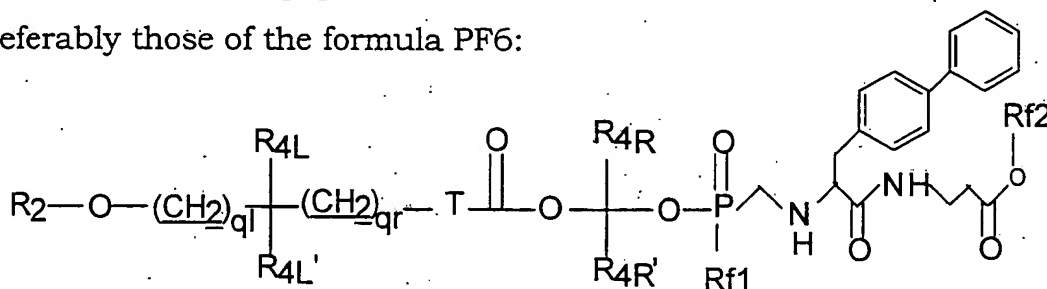


or

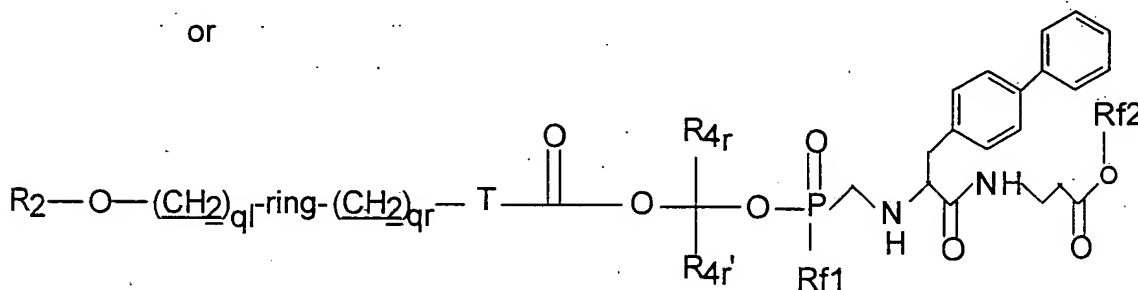


The paragraph beginning on page 88, line 13, has been amended as follows:

- A further phosphonate compound amenable to the prodrugs of the invention are the neutral endopeptidase inhibitors such as CGS-24592 (Novartis), preferably those of the formula PF6:



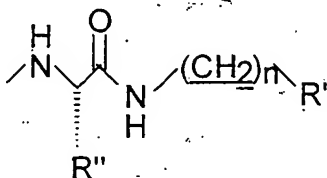
or



where RF1 is H or a further structure of formula II''b

The paragraph beginning on page 100, line 21, has been amended as follows:

Disclosed embodiments of Formula II for the A'/A'' groups of the compounds of formula I include those of the formula IIa:

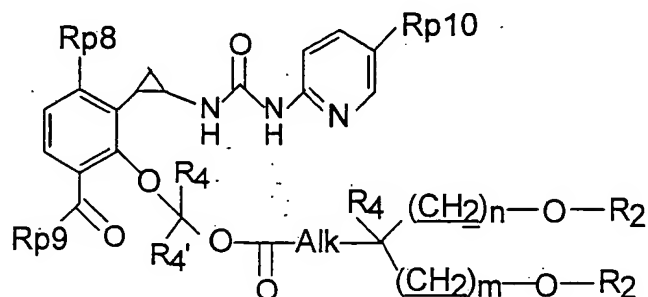


IIa

where n is 1 or 2 and R' is alkyloxy, preferably methyloxy, or those where n is 0 and R' is methyl.

The paragraph beginning on page 130, line 18, has been amended as follows:

One variant of a branched Alk^b in Formula P5 can be substituted with hydroxy which in turn is esterified with a further R², thus defining a linker of the formula IIa, as depicted in Formula P6:

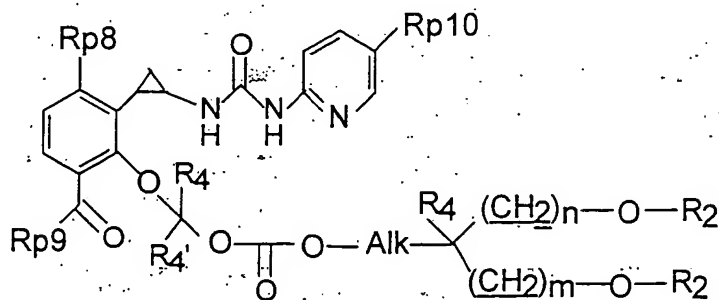


P6

where Rp8, Rp9, Rp10, Alk, R₄, R₄', m, n and R₂ are as defined above. Preferably each occurrence of Rx and Rx' is H. Particularly favoured values for Alk, m and n include: methylene:1:1 and absent: 1:0 respectively.

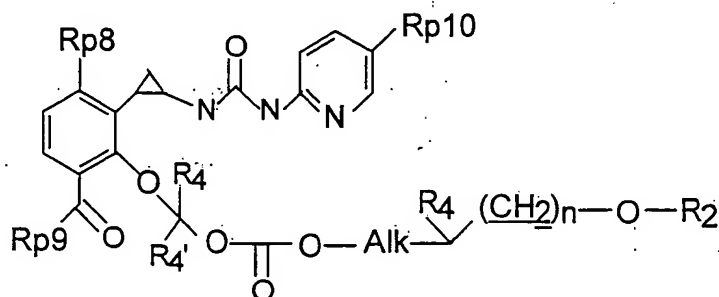
The paragraph beginning on page 131, line 1, has been amended as follows:

A further favoured group of compounds has the Formula P7:



P7

where Rp8, Rp9, Rp10, Alk, R4, R4', m, n and R2 are as defined above or wherein the $-(O)_m-O-R_2$ arm is absent. Preferably each occurrence of Rx and Rx' is H. Particularly favoured values for Alk, m and n include: absent:1:1, thus defining a glycerol derivative. Where the $-(O)_m-O-R_2$ arm is absent to define a structure of the formula P7':

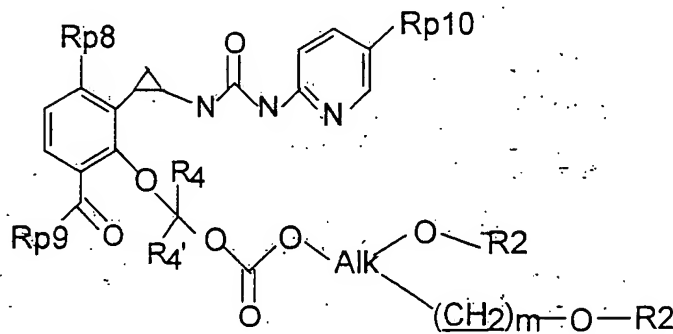


P7'

Convenient values for Alk and n include absent:1 with R4, R4 and R4' as H.

The paragraph beginning on page 134, line 2, has been amended as follows:

As with Formula P5/P6 and P7/P7', Alk^b in formula P8 can comprise an additional $-O-R_2$ substitution to define a compound of the formula P8'

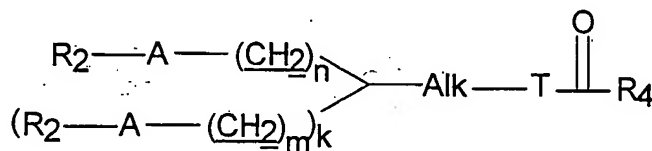


P8'

where each of the variables is as defined above.

The paragraph beginning on page 138, line 18, has been amended as follows:

A still further aspect of the invention provides novel R₂ bearing linkers suitable for derivatisation to free functions on a Drug. Preferred linkers in accordance with this aspect of the invention include compounds of the Formulae IVa:

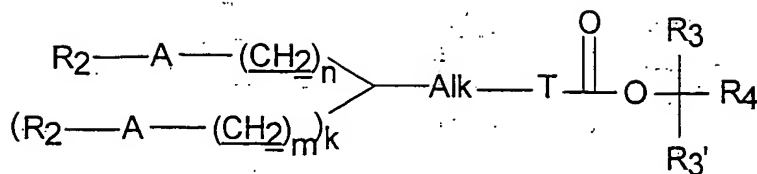


IVa

where R₂, A, A', n, m, Q, Alk, k and T are as defined above and R₄ is hydroxy or an activating group such as an acid derivatives including the acid halide, such as the chloride, anhydrides derived from alkoxy carbonyl halides such as isobutyloxycarbonylchloride and the like, N-hydroxysuccinamide derived esters, N-hydroxyphthalimide derived esters, N-hydroxy-5-norbornene-2,3-dicarboxamide derived esters, 2,4,5-trichlorophenol derived esters and the like. Compounds of Formula IVa will be particularly useful for Drugs bearing hydroxy or amine functions.

The paragraph beginning on page 139, line 1, has been amended as follows:

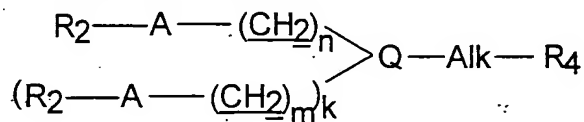
Further preferred linkers in accordance with this aspect of the invention include compounds of the formulae IVe:



IVe

where R₂, A, A', n, m, Q, Alk and T are as defined above, and R₄ an activating group such as a halide, including bromo, chloro and iodo. Compounds of Formula IVe will be especially useful for Drugs bearing carboxy functions (especially those where T is O, R₃ is Me and R₃' is H) or phosphonyl functions (especially those where T is a bond, R₃ is isopropyl and R₃' is H).

Alternative preferred di- or trifunctional linker compounds of this aspect of the invention include compounds of the Formulae IIIa:



IIIa

where R₂, A, A', n, m, Q and Alk are as defined above and R₄ is hydroxy or an activating moiety such as halo, including chloro, iodo and bromo.